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Effect of a flooding dose of leucine in stimulating incorporation of constantly infused valine into albumin.

Smith K, Downie S, Barua JM, Watt PW, Scrimgeour CM, Rennie MJ.

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Recently, we demonstrated increased incorporation of [13C] valine tracer into muscle protein after administration of a flooding dose of L-leucine. We have now investigated the possibility of a similar effect on albumin synthesis in the same group of volunteers. We gave L-[1-13C]leucine (20 atom%, 0.05 g/kg) during the final 90 min of a 7.5-h primed constant infusion of L-[1-13C]valine (99 atom%, 1.5 mg/kg prime constant infusion of 1.5 mg.kg-1.h-1) in healthy male volunteers in the postabsorptive state. Blood samples, taken at 0.5- to 1-h intervals during the constant infusion and at 5- to 30-min intervals during the application of the flooding dose, were analyzed for the concentration and 13C enrichment of leucine, valine, and their ketoacids. Albumin was isolated and hydrolyzed, and the enrichments of incorporated valine and leucine were compared with the mean enrichment of various possible precursor pools to calculate the apparent rate of albumin protein synthesis according to the standard procedures. During constant infusion of [13C] valine tracer the rate of albumin synthesis (measured using alpha-ketoisovalerate labeling as a surrogate for the true precursor) was 0.250 +/- 0.041%/h (SD), a value identical to that routinely obtained using constant leucine tracer infusion and alpha-ketoisocaproate labeling. During the application of the flooding dose of leucine, the rate of incorporation of tracer [13C]valine into albumin increased by 73% to 0.433 +/- 0.129%/h (P < 0.05); the apparent protein synthetic rate calculated from the incorporation of leucine applied during the flood was 0.402 +/- 0.057 (P < 0.001). These results raise further doubts about the validity of the flooding dose method for the measurement of rates of human protein synthesis.

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Relationship of plasma leucine and alpha-ketoisocaproate during a L-[1-13C]leucine infusion in man: a method for measuring human intracellular leucine tracer enrichment. [Metabolism. 1982]

Comparison of constant infusion and flooding dose techniques to measure muscle protein synthesis rate in dogs. [J Nutr. 1992]

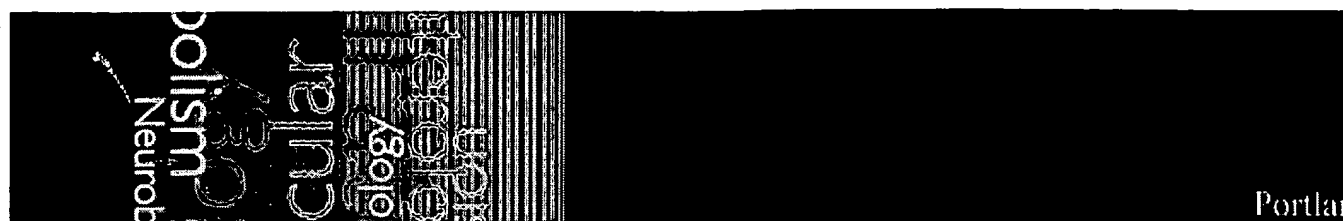
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Clinical Science (2002) 102, (107–114) (Printed in Great Britain)

The response of liver albumin synthesis to infection in rats varies with the phase of the inflammatory process

Benoît RUOT*, Fabienne BÉCHEREAU*, Gérard BAYLE*, Denis BREUILLÉ† and Christiane OBLED*

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Key words: hypoalbuminaemia, infection, liver, protein synthesis.

Abbreviations: ASR, absolute synthesis rate; FSR, fractional synthesis rate; α_1 GPA, α_1 -acid glycoprotein; α_2 M, α_2 -macroglobulin; S_a , specific radioactivity of tissue free valine.

Correspondence: Dr Christiane Obled (e-mail obled@clermont.inra.fr).

To discriminate between the effects of infection and of anorexia associated with infection, liver albumin synthesis was measured in well-fed rats, in rats injected with live *Escherichia coli* and in pair-fed rats at different stages of the inflammatory response (1, 6 and 10 days after infection) using a large dose of L-[1- 14 C]valine. Albuminaemia and albumin mRNA levels were unchanged following food restriction. However, absolute albumin synthesis was decreased in pair-fed rats compared with control animals after 1 day of food restriction, and had returned to normal values by day 10 when food intake was restored. Infection was characterized by a decrease in the plasma albumin concentration (35%, 45% and 28% as compared with pair-fed rats at 1, 6 and 10 days after infection respectively). Albumin mRNA levels and relative albumin synthesis were reduced in infected rats as compared with both control and pair-fed animals at all stages of infection. However, during the early acute response, the albumin absolute synthesis rate was similar in infected rats and pair-fed rats, indicating no specific effect of infection at this stage. Later in the course of infection, the amount of albumin synthesized by the liver was lower in infected than in pair-fed rats, and hypoalbuminaemia was probably maintained due to a lack of stimulation of synthesis despite increased food intake.

Received 12 April 2001/2 July 2001; accepted 4 September 2001

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Increased albumin and fibrinogen synthesis rate in patients with chronic renal failure

Authors: Prinsen, Berthil H.C.M.T.; Rabelink, Ton J.; Beutler, Jaap J.; Kaysen, George A.; De Boer, Jose; Boer, Walther H.; Hagen, E. Christiaan; Berger, Ruud; De Sain-Van Der Velden, Monique G.M.

Source: Kidney International, Volume 64, Number 4, October 2003, pp. 1495-1504(10)

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Abstract:

Increased albumin and fibrinogen synthesis rate in patients with chronic renal failure. Background.

Hypoalbuminemia and hyperfibrinogenemia are frequently observed in patients with chronic renal failure (CRF) and are both associated with cardiovascular diseases. The mechanisms responsible for hypoalbuminemia and hyperfibrinogenemia in CRF are unknown. Methods.

In the present study, both albumin and fibrinogen kinetics were measured in vivo in predialysis patients ($N = 6$), patients on peritoneal dialysis ($N = 7$) and control subjects ($N = 8$) using $[1-^{13}\text{C}]$ -valine. Results.

Plasma albumin concentration was significantly lower in patients on peritoneal dialysis compared to control subjects ($P < 0.05$). Plasma fibrinogen was significantly increased in both predialysis patients ($P < 0.01$) as well as patients on peritoneal dialysis ($P < 0.001$) in comparison to control subjects. In contrast to albumin, fibrinogen is only lost in peritoneal dialysate and not in urine. The absolute synthesis rates (ASR) of albumin and fibrinogen were increased in patients on peritoneal dialysis (ASR albumin, 125 ± 9 mg/kg/day versus 93 ± 9 mg/kg/day, $P < 0.05$; ASR fibrinogen, 45 ± 4 mg/kg/day versus 29 ± 3 mg/kg/day, $P < 0.01$) compared to control subjects. Albumin synthesis is strongly correlated with fibrinogen synthesis ($r^2 = 0.665$, $P < 0.0001$, $N = 21$). In this study, the observed hypoalbuminemia in patients on peritoneal dialysis is likely not explained by malnutrition, inadequate dialysis, inflammation, metabolic acidosis, or insulin resistance. We speculate that peritoneal albumin loss is of relevance. Conclusion.

Synthesis rate of albumin and fibrinogen are coordinately up-regulated. Both albumin and fibrinogen are lost in peritoneal dialysis fluid. To compensate protein loss, albumin synthesis is up-regulated, but the response, in contrast to predialysis patients, does not fully correct plasma albumin concentrations in peritoneal dialysis patients.

The increase in fibrinogen synthesis introduces an independent risk factor for atherosclerosis, since plasma fibrinogen pool is enlarged.

Keywords: albumin; fibrinogen; renal failure; peritoneal dialysis; hypoalbuminemia; hyperfibrinogenemia; amino acids

Document Type: Research article

DOI: 10.1046/j.1523-1755.2003.00211.x

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Dynamic response of immobilized cells to pulse addition of L-valine in cyclosporin A biosynthesis.

Chun GT, Agathos SN.

Department of Chemical and Biochemical Engineering, Rutgers-State University of New Jersey, Piscataway.

A feeding strategy for L-valine was tested in the production of cyclosporin A (Cy A), a powerful immunosuppressive secondary metabolite, in celite-immobilized cells of the fungus *Tolypocladium inflatum*. This system has been previously shown to have promise over conventional submerged systems. Significant increase in Cy A biosynthesis was manifested in the immobilized cells when L-valine was added at 108 h (system C) and at 156 h (system D) during the exponential growth phase. However, no clearly stimulating effect of L-valine on Cy A titre was observed when the amino acid was supplemented at hour 60 (lag phase, system B) or when the valine was present from the start (system A), where system A = 100%, system B = 113%, system C = 253%, system D = 302%. The large contribution to the enhanced production of Cy A in systems C and D may be explained by the preferential channeling of L-valine to growth during the lag phase and to secondary metabolism during the late exponential phase of the immobilized cells.

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L-Tryptophan injection enhances pulsatile growth hormone secretion in the rat

MA Arnold and JD Fernstrom

The effect of injecting L-tryptophan or a serotonin receptor agonist [6-Cl-2-[1-piperazinyl]pyrazine ((MK0212)) on pulsatile GH secretion was studied in male rats bearing right atrial cannulae. After injection, blood samples were drawn at 15-min intervals for periods up to 4 h. L-Tryptophan administration (50 or 100 mg/kg, ip) significantly enhanced mean plasma GH levels measured over a 3.5-h period.

Injection of another large neutral amino acid, L-valine (100 mg/kg, ip), did not influence plasma GH levels. However, when administered with tryptophan, valine blocked the tryptophan-induced enhancement of GH secretion and blunted the increases in brain tryptophan and serotonin levels that normally accompany tryptophan injection. Injection of MK-212 (2 mg/kg, ip) elicited an immediate rise in plasma GH levels; this effect was completely blocked by pretreatment with metergoline (2 mg/kg, ip), a serotonin receptor antagonist. Taken together, these data support the notion that treatments which increase serotonin receptor stimulation enhance or induce pulsatile GH secretion.

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